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Toxicity and Residue Studies in Dairy Animals with FireMaster FF-1 (Polybrominated Biphenyls)

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Two studies (one in Holstein calves and one in Holstein cows) were conducted to determine potential toxicity and residue levels following oral ingestion of polybrominated biphenyls (PBB). The material was FireMaster FF-1. Administration was by gelatin capsules. Doses in calves were 0.1, 1.0, 10, or 100 mg/kg body weight, while doses in cows were equivalent to 0.01, 0.1, 1.0, or 10 ppm in the diet.

The calves were sacrificed after 2, 4, 6, or 12 weeks. The cows were fed 158 or 228 days, and were then in a recovery period for 182 or 112 days.

In the calf study, signs of toxicity were observed only in animals fed 100 mg/kg-day. Administration of 10 mg/kg-day or less for up to 12 weeks caused no overt signs of toxicity. Histologic studies were conducted upon selected organs and tissues taken at time of sacrifice. The only treatment-induced lesions among animals fed 0.1 mg/kg-day were minimal lesions in the kidney and skin in the one calf fed at this level for 12 weeks. Treatment-induced lesions were present in the kidneys, skin, and/or liver from some animals fed levels of 1.0 mg/kg-day and above. The relative severity of these lesions was related to the level and length of exposure. Treatment-associated changes were observed in the testes of all males in this study. The hypospermatogenesis observed was consistent with the age of the animals due to prepuberal development of the testes. No clinical signs of toxicity or histologic changes attributed to PBB were observed in the cows. Two cows were pregnant at the initiation of the study and give birth to normal, healthy calves during the study. These calves grew normally and appeared healthy when sacrificed at about 6 months of age.

Residue levels were quantitated as the hexabromobiphenyl isomer (BP-6) which is the major isomer present in the PBB mixture. Tissue residue levels in calves increased with dose and duration of administration of PBB with highest levels being found in the fat. At 100 mg/kg the levels in fat were about 6000 to 6300 ppm after 6 to 12 weeks.

Residue levels of BP-6 in milk and fat of the cows also increased with dose and duration of administration. Maximum levels in milk were about 1/3 the levels in the diet. In general, the levels plateaued after about 4 to 6 weeks and did not go appreciably higher even though administration of the FireMaster FF-1 was continued. Maximum levels in fat were on the order of approximately 4.5 times the levels in the diet, except at the lowest dose level.

Residues decreased in milk after administration of PBB was discontinued, but detectable levels were still present 6 months later. Residues were found in the calves born of treated cows indicating passage of the PBBs through the placental barrier and/or ingestion through the milk.

Introduction

Toxicity attributed to polybrominated biphenyls which accidentally contaminated feed of dairy cattle was described by Jackson and Halbert (*1*). Therefore, the two studies reported here were initiated. The primary purpose of these studies was to study possible toxicity and residue levels following oral administration of known doses of the material. Since these studies were conducted, a study of toxicosis from polybrominated biphenyls in heifers has been reported by Moorhead et al. (*2*).

One of the studies was conducted to evaluate the potential toxic effects and to determine tissue residues following oral administration to Holstein calves. The other study was conducted to evaluate potential toxicity and to determine residue levels in milk, urine, feces and tissues following oral administration to mature Holstein cows.

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Materials

The polybrominated biphenyls were fed as FireMaster FF-1, which is a pulverized form of FireMaster PB-6 with 2% calcium trisilicate added to prevent caking.

FireMaster BP-6 is a mixture of brominated biphenyls with about 65% hexabromobiphenyls, 14% heptabromobiphenyls, 11% pentabromobiphenyls, and about 10% other biphenyls. Chemical analyses were for BP-6.

Methods

Calves

There were eight male and eight female Holstein calves, weighing 98 to 169 kg at the start of the study. Each calf was housed individually for 14 days prior to the start of the investigation.

The animals were divided into four groups of two males and two females each. Each group received daily oral doses of PBB in gelatin capsules, at dose levels of 0.1, 1.0, 10, or 100 mg/kg body weight/day. These doses are equivalent to about 3.3, 33, 330, or 3300 ppm in the diet.

All calves were weighed each week, and the most recent weight was used for dose calculations. They were fed 1 kg of 16% grain ration daily. Hay and water were allowed *ad libitum*.

The calves were examined daily for signs of overt clinical toxicity.

The following determinations were conducted upon each calf just prior to the inception of the study and weekly thereafter: hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, blood urea nitrogen (BUN), blood glucose, serum alkaline phosphatase (SAP), serum glutamic-pyruvic transaminase (SGPT), and serum glutamic-oxalacetic transaminase (SGOT).

One animal (male) from each group was sacrificed after 2 weeks of testing, one additional animal from each group (female) was sacrificed after 4 weeks, and after 6 weeks a third animal (male) from each group was sacrificed. The remaining female from each group was sacrificed after 12 weeks of testing. All major tissues and organs were examined grossly at time of sacrifice. The following tissues and organs were examined histologically: adrenal glands, brain, pituitary, gonads, heart, kidneys, liver, lungs, skin, spleen and thyroids.

Samples of liver, kidney, fat, and skeletal muscle taken from each animal at sacrifice were analyzed for BP-6 content.

Cows

Eight Holstein cows were used. Each cow was individually stanchioned for 14 days prior to the start of the investigation. All animals were in good health, mastitis-free, and tested TB- and Brucellosis-negative.

They were divided into four groups of two cows each. Each group received daily oral doses of PBB in gelatin capsules, equivalent to 0.01, 0.1, 1, or 10 ppm in the diet (based on a daily food consumption of 17 kg per cow). The total daily food consumption was 4.5 kg of a 16% grain ration and approximately 12.5 kg of clover-prairie hay daily; water was permitted *ad libitum*. The levels were equivalent to about 0.0003, 0.003, 0.03, or 0.3 mg/kg body weight per day.

The material was administered for 158 consecutive days to six of eight cows and for 228 consecutive days to the other two cows. The latter two cows (No. 2, 0.01 ppm and No. 6, 1 ppm) were pregnant. Therefore, administration was continued until their calves were about 2 months old. Administration of PBB was discontinued and the cows were placed on recovery for 182 days (6 cows) or 112 days (2 cows). The total duration of the experiment was 340 days.

Total daily milk production was recorded throughout the investigation. Initial, weekly and final body weights were recorded throughout the investigation. Observations for mortality, general behavorial reactions and pharmacotoxic signs were conducted daily.

The following determinations were conducted upon each cow just prior to the inception of the study and weekly (new calves, too) thereafter, hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte counts, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, blood urea nitrogen (BUN), blood glucose, serum alkaline phasphatase (SAP), serum glutamic-pyruvic transaminase (SGPT), serum glutamic-oxalacetic transaminase (SGOT), albumin, glucose, pH, microscopic examinations leukocyte-erythrocyte. Thyroid function tests, T-3 or triiodothyronine by resin uptake, T-4 or thyroxine by column and free thyroid index by calculation, were conducted 3 weeks before the end of the study in the cows.

At the end of the investigation the animals were sacrificed. All major tissues and organs were examined grossly during the necropsy. Specimens of the following tissues were preserved in 10% neutral buffered formalin for histological examination: adrenal gland, brain, bronchial lymph node, gall bladder, gonads, heart, kidneys, liver, lung, pituitary, spleen, thyroids, and bone with marrow.

Milk samples were collected weekly during the test period, with the collections for the first 90 days analyzed for BP-6. Weekly milk samples also were collected and analyzed during the recovery period. Blood, urine, and feces were collected weekly for the first 90 days and analyzed for BP-6. Samples of liver, kidney, fat, skeletal muscle, and bone were obtained at sacrifice for analysis of BP-6 content.

Extraction and clean-up techniques were developed and optimized for each type of sample to be analyzed. Gas-liquid chromatography (Tracor MT-220 gas-chromatograph with a ^{63}Ni detector) was used to quantitate residues.

The analytical methods for milk, blood, fat, bone marrow, feces, and urine were validated by analyzing control tissues fortified at the limit of sensitivity of each method with BP-6 analytical standard. The recoveries obtained average 100% for milk at 1 ppb, 98% for blood at 5 ppb, 100% for fat and bone marrow at 50 ppb, 76% for feces at 5 ppb, and 84% for urine at 5 ppb. The highest fortification level made in fat was at 150 ppm, 93% recovery was obtained. The precision of analysis of selected tissues was determined by analyzing six aliquots of each tissue type after homogenization and fortification at the limit of sensitivity. Relative standard deviations of less than 9% were obtained.

Results

Calves

Generally, poor weight gains or body weight losses were noted among animals at the 100.0 mg/kg level. Two calves (male 14 and female 15) lost 8 kg each, while a third calf (female 16) lost 22 kg. All calves in the other groups had normal weight gains.

Calves 14 and 16 (100 mg/kg) had decreased food consumption from test day 36 until sacrifice. There were no other differences in food consumption values among calves at any other level.

No deaths occurred. On test day 21, calf 15 (100 mg/kg) became lethargic and remained in this condition until it was sacrificed on day 28. Calves 14 and 16 (both 100 mg/kg) had signs of keratitis, and lacrimination beginning on day 35 which continued until time of sacrifice. In addition, on test day 50, calf 16 developed alopecia and hyperkeratosis involving the head, cervical, and dorsal thoracic region that progressed in severity until sacrificed.

Although slightly elevated from day 21, the elevated total leukocyte count was apparent on test days 77 and 84 (weeks 11 and 12) for female 16 at the 100 mg/kg level. Additionally, differential leukocyte counts revealed a reverse lymphocyte-neutrophil ratio from day 42 which was especially noticeable on test day 84, when it was sacrificed. Values for all other hematologic parameters were essentially the same among the other groups.

There were increases in SGOT and BUN values during the final 2 weeks (days 77 and 84) in blood from the animal (female 16) fed 100 mg/kg. In the same calf there were decreased SAP values after day 49. Male 14 (100 mg/kg) also had lower SAP values on days 35 and 42, at which time he was sacrificed. Values for all other animals were comparable and considered normal among groups for the clinical chemistry parameters investigated.

The histopathological evaluation of a series of tissues from the 16 calves revealed treatment-induced lesions in the kidney, liver, and skin. Lesions were also observed in the testes which were treatment-associated and ascribed to several factors including the nutritional status, age of the animal (prepuberal development), and duration of exposure to PBB. One or more of the above tissues were affected in animals from all test groups. The relative severity of the treatment-induced lesions was related to dose level and length of exposure to the test material.

The treatment-related renal lesions comprised a wide spectrum of degenerative changes which represent various stages in the development of tubular nephrosis. The most severe lesions were present in female 16 which was exposed at the highest dose level (100 mg/kg) for 12 weeks. The renal lesions observed among animals exposed at the lower test dose levels for shorter periods of time were of lesser severity (minimal) and they consisted of focal dilatation of cortical tubules. Some affected tubules contained exfoliated epithelial lining cells within their lumen. Among animals at the higher dose levels or those exposed for a longer period of time, the tubular dilatation was slightly more severe, more extensive and was accompanied by regeneration of tubular epithelial cells. Some of the affected tubules also contained proteinaceous or granular casts mixed with cellular debris. Lesions of interstitial fibrosis and compression of glomeruli were also present in the kidney from calf 16.

Treatment-related hepatic lesions were confined to animals in groups fed 1, 10, or 100 mg/kg. Two animals (Nos. 6 and 8) at the 1 mg/kg level that were exposed to the test material for 6 to 12 weeks, respectively, had foci of slightly enlarged hepatocytes located in the centrilobular region of some lobules. The enlargement of hepatocytes was due to an increase in cytoplasmic mass with no nuclear changes. However, there was no significant increase in the liver weights of these animals. This lesion was not evident among animals at other dose levels. The liver of one female (No. 11) at the 10 mg/kg level and two females (Nos. 14 and 16) at the

100 mg/kg level revealed degeneration and/or necrosis of individual or small foci of hepatocytes with no lobular distribution. The necrosis of hepatocytes was accompanied by liver cell regeneration among those animals fed 100 mg/kg of PBB.

Treatment-related skin lesions were present among single female animals at 0.1 mg/kg (No. 4), 10 mg/kg (No. 12), and 100 mg/kg (No. 16) levels exposed for 12 weeks to PBB. These changes consisted of either acanthosis, hyperkeratosis and/or dermal infiltrates of mononuclear cells. The changes were similar in nature among all three animals but they were most severe in animal No. 16.

Treatment-associated changes were present in the testes and epididymides of all males in this study. The changes described as hypospermatogenesis of the testes and the absence of sperm in epididymal ducts are consistent with the age of these animals due to prepuberal development. Degeneration of the germinal epithelial cells lining seminiferous tubules was also present in many of these bull calves. The severity of the degenerative change was variable but may have resulted from impairment in the nutritional status of these animals rather than a direct effect of the test material.

Other lesions found were attributed to naturally occurring diseases or related to the method of sacrifice.

Samples of liver, kidney, fat, and muscle obtained from each calf at the time of sacrifice were analyzed for BP-6 residues. The results of the analysis are presented in Table 1.

The tissue residue concentrations of BP-6 were directly related to the dose level and the period of exposure. The highest levels of BP-6 were found in the fat. Lower levels were found in kidneys, liver, and muscle.

Cows

Milk production ranged from 7.6 to 31.4 lb/day prior to administration of the PBB. The production in two cows (Nos. 2 and 6) dropped considerably prior to parturition. After calving, even though administration of PBB continued, their production increased to about 30 lb/day for cow 2 and 50 lb/day for cow 6. Milk production was decreased in all cows during the latter part of the recovery period. This is consistent with the normal state and cycle of lactation.

The body weights of the cows ranged from 446 to 591 kg at the start of the study. All animals gained weight during the study. The two pregnant cows lost weight after delivery, as would be normally expected after parturition. The two calves weighed 46 and 50 kg, respectively, at birth. They had normal weight gains and at about 6 months of age they both weighed 229 kg.

There were no differences in food consumption values among cows at any levels. All were considered normal in this respect.

No deaths occurred during the investigation. The following reactions were observed. On day 71, cows 2 (0.01 ppm) and 5 and 6 (1 ppm) were stomping their fore and hindfeet and appeared uncomfortable. This lasted until test day 86 for cow 2 and day 75 for cows 5 and 6. On test day 240, a subcutaneous accumulation of fluid (about 200 ml) was observed over the right rib cage of cow 2. The fluid began to subside on test day 149 and was no longer evident

Table 1. Toxicity and tissue residue study in dairy calves: FireMaster FF-1 residues in tissue.

Dose mg/kg body weight/day	Calf (number and sex)	Time on test, weeks	Time concentration of PBB, ppm			
			Muscle	Fat	Liver	Kidney
0.1	1—M	2	0.088	2.56	0.475	0.091
	2—M	6	0.119	7.50	0.809	0.419
	3—F	4	0.038	7.31	1.43	0.418
	4—F	12	0.059	15.8	1.48	0.751
1.0	5—M	2	0.049	18.8	1.21	2.10
	6—M	6	0.250	42.5	1.54	2.92
	7—F	4	0.244	27.5	1.54	0.987
	8—F	12	0.450	58.8	2.61	2.47
10.0	9—M	2	0.694	104.4	2.63	11.8
	10—M	6	1.39	241.9	4.13	20.9
	11—F	4	1.26	378.0	4.63	20.8
	12—F	12	1.84	810.0	6.88	23.3
100.0	13—M	2	15.5	1,010	75.9	90
	14—M	6	33.8	6,080	106	201
	15—F	4	32.1	4,050	135	203
	16—F	12	33.8	6,330	550	683

by day 157. On day 129, cow 5 had slight overgrowth of the hooves involving all feet which increased in severity for the remainder of the investigation.

Hematologic data revealed no treatment-related changes among any of the parameter investigated. Cow 6 had an elevated total leukocyte count throughout the study with lymphocytes comprising a high percentage of the cells.

Clinical chemistry values were normal and reflected no changes related to treatment in any of the cows or in the two calves. The values obtained for thyroid function were considered to be normal for cattle of this age. These values compare favorably with those reported for Holstein cows in another study (*3*).

The results of the analyses for residues of BP-6 in milk are presented in Tables 2 and 3. The residues increased as the dose increased (0.01 ppm through 10 ppm in the diet). In general, the levels plateaued after about 4 to 6 weeks and did not go appreciably higher even though administration of the FireMaster FF-1 was continued.

Maximum levels of BP-6 found in milk in relation to levels in the diet were about 0.06, 0.07, 0.03, and 3 ppm at 0.01, 0.10, 1.0, and 10 ppm in the diet, respectively. After administration of FireMaster FF-1 was stopped, the levels of BP-6 in milk were observed to decrease rather slowly. Some BP-6 was still detectable in milk from animals of all groups after the recovery period (approximately 6 months).

In most cases BP-6 was not detected in urine (limit of detection 0.005 ppm) after 90 days of administration, even at 10 ppm of PBB in the diet.

BP-6 was barely detectable in feces from some cows fed 0.01 ppm. Levels in feces in cows at other dose levels were about 0.02, 0.15 or 1.5 ppm at 0.1, 1.0 or 10 ppm in the diet, respectively. It appears that about 15% of the ingested dose is excreted in the feces.

Residues in blood were detected (lower limit 0.01 ppm) only in cows fed 10 ppm. The levels of BP-6 in their blood were in the order of 0.05 to 0.1 ppm.

The residues in bone marrow and fat from three sites (tail, stomach and brisket) for the cows and calves at sacrifice are presented in Table 4. The

Table 2. Milk residue study in diary cattle: residue levels of PBB in milk in test period.

Cow No.	Daily diet level, ppm	Concentration of PBB, ppm																
		Day 0	Day 3	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56	Day 63	Day 70	Day 77	Day 84	Day 91	Day 166	Day 229
1	0.01	0.001	0.002	0.004	0.007	0.005	0.004	0.048	0.067	0.052	0.027	0.030	0.023	0.021	0.018	0.015	[a]	[a]
2	0.01	0.001	0.002	0.003	0.004	0.004	0.004	0.045	0.063	0.037	0.022	0.024	0.023	0.026	0.025	0.022	0.011	0.027
3	0.1	0.001	0.004	0.015	0.019	0.025	0.017	0.054	0.048	0.033	0.016	0.035	0.031	0.030	0.030	0.028	[a]	[a]
4	0.1	0.001	0.010	0.028	0.037	0.039	0.028	0.106	0.058	0.059	0.036	0.049	0.042	0.066	0.049	0.048	[a]	[a]
5	1.0	0.001	0.260	0.260	0.265	0.269	0.219	0.226	0.270	0.299	0.280	0.315	0.393	0.265	0.342	0.278	[a]	[a]
6	1.0	0.001	0.072	0.192	0.240	0.227	0.196	0.176	0.226	0.275	0.210	0.305	0.239	0.269	0.218	0.205	0.263	0.258
7	10.0	0.001	1.75	1.91	2.18	1.32	2.14	2.29	2.40	2.70	2.44	3.00	2.39	2.78	2.65	2.70	[a]	[a]
8	10.0	0.001	1.78	1.56	1.80	1.82	2.02	1.44	2.25	2.38	2.02	2.40	2.25	2.00	2.36	2.25	[a]	[a]

[a] Samples not taken.

Table 3. Milk residue study in dairy cattle: residue levels of PPB in milk in recovery period.

Cow No.	Daily diet level, ppm	Concentration of PBB, ppm												
		Recovery day 0	Recovery day 1	Recovery day 3	Recovery day 7	Recovery day 14	Recovery day 28	Recovery day 30	Recovery day 60	Recovery day 70	Recovery day 100	Recovery day 112	Recovery day 130	Recovery day 183
1	0.01	0.030	0.030	0.010	0.010	0.012	0.011	[a]	[a]	0.009	0.008	[a]	0.008	0.004
2	0.01	[a]	[a]	[a]	[a]	[a]	[a]	0.011	0.018	[a]	[a]	0.015	[a]	[a]
3	0.1	0.015	0.032	0.010	0.010	0.010	0.018	[a]	[a]	0.016	0.010	[a]	0.013	0.010
4	0.1	0.043	0.045	0.028	0.024	0.027	0.020	[a]	[a]	0.016	0.011	[a]	0.015	0.009
5	1.0	0.383	0.380	0.224	0.199	0.199	0.158	[a]	[a]	0.125	0.088	[a]	0.141	0.071
6	1.0	[a]	[a]	[a]	[a]	[a]	[a]	0.108	0.065	[a]	[a]	0.065	[a]	[a]
7	10.0	2.63	2.85	1.310	1.80	1.93	1.43	[a]	[a]	1.20	0.868	[a]	0.587	0.550
8	10.0	1.61	2.21	0.450	0.788	0.917	0.80	[a]	[a]	0.85	0.682	[a]	0.527	0.525

[a] Samples not taken.

Table 4. Meat and milk residue study in dairy cattle: residue levels of PBB in fat and bone marrow.

Animal No.	Daily diet level, ppm	Sacrifice on recovery day	Concentration of PBB, ppm			
			Tail fat	Stomach fat	Brisket fat	Bone marrow
Cow 1	0.01	182	0.244	0.331	0.319	0.519
Cow 2	0.01	112[a]	0.677	0.680	0.703	0.738
Calf 2[b]	—	175[c]	0.640	0.547	0.787	0.880
Cow 3	0.10	182	0.520	0.477	0.457	0.665
Cow 4	0.10	182	0.443	0.282	0.417	0.681
Cow 5	1.0	182	3.27	3.55	4.51	4.38
Cow 6	1.0	112[a]	7.50	5.25	6.61	9.00
Calf 6[b]	—	169[b]	7.50	4.09	7.13	8.13
Cow 7	10.0	182	32.6	28.1	47.8	36.0
Cow 8	10.0	182	46.1	29.7	44.5	48.1

[a] Cows that calved remained on treatment unitl their calves were about 2 months old.
[b] Born to cow with corresponding number.
[c] Age of calf at time of sacrifice.

residue levels, in general, increased as the level of oral intake increased. The two cows with shorter (112 days) recovery periods had higher residues then the other two at the same feeding level with longer (182 days) recovery periods. Levels in the fat were on the order of 50 times the levels in the 0.01 ppm diet and 4.4 times the levels in the 0.1, 1.0, and 10 ppm diets.

Gross and histopathological evaluations were conducted on a series of tissue from the eight cows and two calves. The lesions described were regarded as either those of naturally occurring diseases related to the age of the animal or ascribed to the method of sacrifice. With regard to the latter, there was focal hemorrhage in the lung and brain. The findings in the ovaries were indicative of a normal estrus cycle in the cows.

Discussion and Summary

One of these studies was conducted to evaluate the potential toxic effects and to determine tissue residues of BP-6 after oral administration to Holstein dairy calves. Dose levels of 0.1, 1.0, 10.0, or 100.0 mg/kg were administered daily in gelatin capsules to groups of four calves (two males and two females) for 2 to 12 consecutive weeks. Calves were sacrificed at 2, 4, 6, and 12 weeks. Animals at the highest dose level lost weight and displayed alopecia, keratitis, and lacrimation from test day 35 until their sacrifice. There were increased BUN, SAP and SGPT values at the highest dose. Histopathologic examination of organs and tissues revealed treatment-induced lesions in the kidney, liver and skin which were dose related. Treatment-associated changes were present in the testes among all males. Residue analyses of liver, kidney, muscle, and fat revealed treatment and time related increases in the concentrations of PB-6. Higher concentrations were found in fat than in the other tissues analyzed, with the lowest concentration found in muscle.

The second study was conducted to evaluate potential toxicity and to determine milk and tissue residue levels of BP-6 after oral administration to Holstein dairy cows. Doses were equivalent to 0.01, 0.1, 1.0, or 10.0 ppm in the diet and were also administered in gelatin capsules. The levels were based on a total daily food consumption of 17 kg per cow. Test material was administered daily for 158 consecutive days with the exception of two cows which were pregnant. Those cows received the test material for an additional 70 days. No effects upon milk production, body weights, amount of food consumed, and hematologic clinical chemistry, and urinalysis studies were noted. No deaths occurred. Analysis for BP-6 in milk, blood, feces, urine, and fat revealed a dosage related increase. However, after approximately 4 to 6 weeks of PBB administration the residue levels in milk plateaued and there appeared to be no further accumulation as the residue levels remained relatively constant. Gross and histopathologic studies conducted on all cows revealed no treatment-related lesions. Two cows were pregnant when the study was initiated. These cows were treated during pregnancy and allowed to calve. No problems occurred at parturition, and both calves were normal in appearance and healthy from birth to sacrifice. Though neither calf was treated, tissue residue analysis for BP-6 showed its presence, indicating the passage of the compound through the placental barrier and/or ingestion through the milk.

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